REMARKS

Favorable reconsideration of this application as presently amended is respectfully requested. Claims 1-7, 9-27, 46 and 47 are pending. Claims 1, 9, 13, 14, 26, 46 and 47 are amended. No new matter is added.

Applicants wish to thank Examiner Gabel for conducting several telephone interviews with Applicant's counsel on November 6 and November 7, 2002. As discussed during these Examiner Interviews, Applicant has amended the specification to explicitly provide material from U.S. Patent No. 5,395,588 that was incorporated by reference in the application as originally filed (See p. 14, lines 8-10).

Support for the amendments to the specification are found in the specification at page 14, lines 6-10 where it is stated the preferred types of flow cytometers for use in the present invention are described in U.S. Patent Nos. 5,895,764; 5,824,269; 5,395,588; 4,661,913; the entire contents and disclosures of which were incorporated by reference. In particular, the two paragraphs inserted after page 14, line 16 are taken verbatim from U.S. Patent No. 5,395,588 at column 1, lines 28-59, and are directed to describing the operation of flow cytometers of the type that may be used in the present invention. Therefore, the above amendments to the specification do not add new matter.

Support for the amendment to claim 1 is found in the originally filed specification at page 14, lines 6-10 and the above amendments to the specification.

Based on paragraph 5 of the Office Action, claims 9-10, 26, and 46-47 stand rejected under 35 U.S.C. § 112, second paragraph. Claims 9, 26, 46 and 47 have been amended to clarify what is claimed by claims 9, 26, 46 and 47, respectively. This rejection has thus been obviated by the above amendments to claims 9, 26, 46 and 47.

Based on paragraph 6 of the Office Action, claims 1-3, 5, 7, 9-12, 15-19, and 26-27 stand rejected under 35 U.S.C. 102(b) as being anticipated by Saros *et al.* (U.S. Patent No. 4,853,336) for reasons of record. This rejection is respectfully traversed with respect to the claims as amended.

Claim 1 as currently presented claims the feature of a flow cytometry apparatus that includes a flow cytometer for hydrodynamically focusing of a fluid flow stream and for selectively analyzing particles in each of a plurality of samples as the fluid flow stream passes through the flow cytometer. However, nowhere does Saros *et al.* teach or suggest any means for hydrodynamically focusing a fluid flow stream, much less a flow cytometer for focusing a fluid flow stream.

In addition, although Saros *et al.* may describe the detection of analytes in a liquid sample in a conventional detection system, in the detection device described in Saros *et al.*, the fluids pass through these detection devices in a single bulk phase so that alignment of particles is not an issue and air bubbles are inconsequential. In contrast, in a flow cytometer, the detection device of the present invention, there are 2 fluid phases: a narrow hydrodynamically focused core sample stream that carries the sample particles and an outer sheath stream of much larger volume. Large air bubbles may cause sustained disturbance of the hydrodynamic focusing resulting in sustained misalignment of the sample stream, *i.e.* the sample stream no longer passes precisely through the laser beam; and therefore, a sustained mismeasurement of particle fluorescence may occur. In order to ensure a steady stream of aligned cells, hydrodynamic focusing is required (see Hoy, "An Introduction to Flow Cytometry", copy submitted with Applicants' May 13, 2002 Amendment). Because of the issues with respect to hydrodynamic focusing, it has generally been thought that keeping air out of a fluid flow stream containing particles is extremely important, because the presence of air has been viewed disrupting the alignment of the particles in the fluid

flow stream, thereby making the particles "unmeasurable" by the flow cytometer. In contrast, detection devices other than flow cytometers do not require such focusing and, therefore, have been understood to allow for the presence of air bubbles in a fluid flow stream being analyzed.

Although it may have been known to use air bubbles to separate samples when using detection systems that do not employ a flow cytometer, such as Saros *et al.*, prior to Applicants' invention as claimed in claim 1, it was absolutely not obvious to use an air bubble as a sample separator with a flow cytometer. In fact, in the flow cytometer art it was considered desirable to remove any air bubbles before the air bubbles went through a flow cytometer. However, Applicants have discovered that by controlling the size of air bubbles used to separate samples, the disruption of hydrodynamic focusing may be prevented thereby allowing a flow cytometer to be used with a fluid flow stream containing air bubbles, as claimed by claim 1.

Also, prior to Applicants' invention, as claimed in claim 1, flow cytometers had only been used to analyze one sample at time, because putting buffer fluids between samples did not prevent intermixing and because of the above-described problems with using bubbles to separate samples.

For the reasons discussed above, claim 1 is patentable over Saros *et al.*

Claims 2-3, 5, 7, 9-12, 15-19, 26-27, and 46-47 depend directly or indirectly from claim 1, and, accordingly, include all of the patentable features of claim 1 as well as other patentable features. Therefore, claims 2-3, 5, 7, 9-12, 15-19, and 46-47 are patentable over Saros *et al.* for at least the reasons discussed above with respect to claim 1.

Based on paragraph 7 of the Office Action, claims 4, 6, 13-14, 20-24 and 46-47 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Saros *et al.* in view of Kercso *et al.* (U.S. Patent No. 6,132,685) for the reasons of record (the March 28, 2001, Office Action). This rejection is respectfully traversed.

Claims 4, 6, 13-14, 20-24 and 46-47 are dependent on claim 1, either directly or indirectly, and, therefore, include claim 1's patentable features of using a flow cytometer for selectively analyzing particles in each of a plurality of samples, separated from each other by a separation gas, as the fluid flow stream passes through the flow cytometer. Kercso *et al.* is only cited for showing the use of "multiwell microtiter plates" and microfluidic channels "fabricated on [a] planar substrate comprising polymeric materials which are inherently hydrophobic such as polyvinylchloride (PVC) and polyurethane" as set forth in the March 28, 2001, Office Action at pp. 6-7. (The March 28, 2001, Office Action provides the "reasons of record" referred to in the rejection set forth at paragraph 4 of the September 13, 2001, Office Action). Therefore, Kercso *et al.* cannot remedy the deficiency of Saros *et al.* with respect to failing to describe or show the use of a flow cytometer used for analyzing particles in each of a plurality of samples in a fluid flow stream. Therefore, claims 4, 6, 13-14, 20-24 and 46-47 are patentable over the combination of Kercso *et al.* and Saros *et al.*

Based on paragraph 8 of the Office Action, claim 25 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Saros *et al.* in view of Kercso *et al.* and in further view of Farrell *et al.* (U.S. Patent No. 5,788,927) for the reasons of record (the March 28, 2001, Office Action). This rejection is respectfully traversed.

Claim 25 is indirectly dependent on claim 1 and therefore includes claim 1's patentable features of using a flow cytometer for selectively analyzing particles in each of a plurality of samples, separated from each other by a separation gas, as the

fluid flow stream passes through the flow cytometer. Farrell *et al.* is only cited for suggesting an inverted mounting design of a well plate (See March 28, 2001, Office Action, p. 11). Therefore, Farrell *et al.* does not remedy the deficiencies of the combination of Kercso *et al.* and Saros *et al.* with respect to failing to describe or show the use of a flow cytometer used for analyzing particles in each of a plurality of samples in a fluid flow stream. Therefore, claim 25 is patentable over the combination of Farrell *et al.* with Kercso *et al.* and Saros *et al.*

Based on paragraph 9 of the September 13, 2001, Office Action, claims 1-3, 8-12, 15-19, and 26-27 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Parce *et al.* (U.S. Patent No. 6,150,180) in view of Hach *et al.* (U.S. Patent No. 4,053,282) or Trinel *et al.* (U.S. Patent No. 4,116,631) for the reasons of record (the March 28, 2001, Office Action). This rejection is respectfully traversed with respect to the claims as amended.

In the Office Action the following is stated with respect to justifying combining Hach *et al.* or Trinel *et al.* with Parce *et al.*:

> One of ordinary skill in the art at the time of the instant invention would have a reasonable expectation of success in substituting air to separate individual samples for analysis in flow analyzers or microfluidic systems such as taught by Hach or Trinel for the spacer buffer or separation fluid in the flow channels taught by Parce because Hach and Trinel specifically suggested that separation gas, when incorporated into proper tubing materials an parameter requirements, provides adequate separation between sequential samples so as to prevent contamination or carry-over therebetween. (See September 13, 2001, Office Action, p. 7)

The above-quoted statements used as a basis for combining Hach *et al.* or Trinel *et al.*

with Parce *et al.* indicate that the combination of Hach *et al.* or Trinel *et al.* with Parce *et al.* is *prima facie* improper. The above statements cite no portion of Parce that would supply a person of ordinary skill in the art with a motivation to combine the teachings of Hach *et al.* or Trinel *et al.* with the teachings of Parce *et al.* As stated by the Federal Circuit in *Sibia Neurosciences Inc. v. Cadus Pharmaceutical Corp.* 55 USPQ2d 1927, 1931 (Fed. Cir. 2000), "the factual underpinnings of obviousness include whether a reference provides a motivation to combine its teachings with another," citing *Tec Air, Inc. v. Denso Mfg.*, 52 USPQ2d 1296, 1298 (Fed. Cir. 1999). Accordingly, the teachings of Hach *et al.* or Trinel *et al.* may not be properly combined with the teachings of Parce *et al.*

Also, the above-quoted statements fail to provide a motivation for combining the teachings of Parce *et al.* with Hach *et al.* or Trinel *et al.* The fact that Hach *et al.* and Trinel *et al.* may suggest that separation gas may provide adequate separation between sequential samples provides no motivation for the person of ordinary skill in the art to combine Parce *et al.*'s high throughput screening assay with Hach *et al.*'s method and apparatus for sampling impure water or Trinel *et al.*'s method for microbiological analysis of liquid mediums.

Based on the above-quoted statements, the rejection of claims 1-3, 8-12, 15-19, and 26-27 based on Parce *et al.* in view of Hach *et al.* or Trinel *et al.* improperly relies on Applicants' specification and hindsight to provide the "motivation" to combine these cited references. But for reading Applicants' specification, a person of ordinary skill in the art who read Parce *et al.* would have no motivation to look at Hach *et al.* or Trinel *et al.* nor would a person of ordinary skill who read Hach *et al.* or Trinel *et al.* be motivated to look at Parce *et al.* As held in *In re Dembiczak*, "[c]ombining prior art references without evidence of such a suggestion, teaching, or motivation simply takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability—the essence of hindsight. *See, e.g., Interconnect*

Planning Corp. v. Feil, 774 F.2d 1132, 1138, 227 USPQ 543, 547 (Fed. Cir. 1985) ("the invention must be viewed not with the blueprint drawn by the inventor, but in the state of art that existed at that time")." Furthermore, as held in *Sibia Neurosciences v. Cadus Pharmaceutical Corp.*, "[c]are must be taken to avoid hindsight reconstruction by using 'the patent in suit as a guide through the maze of prior art references, combining the right reference in the right way so as to achieve the result of the claims in suit'", citing *Grain Processing Corp. v. American Maize-Product Co.*, 5 USPQ2d 1788, 1792 (Fed. Cir. 1988), *Sibia Neurosciences v. Cadus Pharmaceutical Corp.,* 55 USPQ2d 1927, 1934 (Fed. Cir. 2000).

Based on the above-cited cases, there is no proper motivation to combine the teachings of Hach *et al.* or Trinel *et al.* with Parce *et al.* and the rejection of claims 1-3, 8-12, 15-19, and 26-27 under 35 USC § 103(a) based on a combination of Hach *et al.* or Trinel *et al.* with Parce *et al.* is improper and should be withdrawn.

Also, claim 1 as currently presented claims the feature of a flow cytometry apparatus that includes a flow cytometer for selectively analyzing particles in each of a plurality of samples as a fluid flow stream passes through the flow cytometer. Although the September 13, 2001, Office Action states that "the flow analyzer taught by Parce appears to disclose the same components as the flow cytometer recited in claim 1" (see Office Action, p. 4), in fact, Parce *et al.* neither teaches nor suggests the use of a flow cytometer for analyzing particles, as claimed in claim 1.

Although Parce *et al.* may describe a method of screening test compounds using a conventional detecting system, in the detection device described in Parce *et al.*, the fluids pass through the detection device in a single phase so that alignment of particles is not an issue and air bubbles are inconsequential. In contrast, in a flow cytometer, the detection device of the present invention, there are 2 fluid phases: a narrow hydrodynamically focused core sample stream that carries the sample particles

and an outer sheath stream of much larger volume. Large air bubbles may cause sustained disturbance of the hydrodynamic focusing resulting in sustained misalignment of the sample stream, *i.e.* the sample stream no longer passes precisely through the laser beam; and therefore, a sustained mismeasurement of particle fluorescence may occur. In order to ensure a steady stream of aligned cells, hydrodynamic focusing is required (see Hoy, "An Introduction to Flow Cytometry", copy submitted with Applicants' May 13, 2002 Amendment). Because of the issues with respect to hydrodynamic focusing, it has generally been thought that keeping air out of a fluid flow stream containing particles is extremely important, because the presence of air has been viewed disrupting the alignment of the particles in the fluid flow stream, thereby making the particles "unmeasurable" by the flow cytometer. In contrast, detection devices other than flow cytometers do not require such focusing and, therefore, have been understood to allow for the presence of air bubbles in a fluid flow stream being analyzed.

Although it may have been known to use air bubbles to separate samples when using detection systems that do not employ a flow cytometer, such as Parce *et al.*, prior to Applicants' invention as claimed in claim 1, it was absolutely not obvious to use an air bubble as a sample separator with a flow cytometer. In fact, in the flow cytometer art, it was considered desirable to remove any air bubbles before the air bubbles went through a flow cytometer. However, Applicants have discovered that by controlling the size of air bubbles used to separate samples, the disruption of hydrodynamic focusing may be prevented thereby allowing a flow cytometer to be used with a fluid flow stream containing air bubbles, as claimed by claim 1.

Also, prior to Applicants' invention as claimed in claim 1, flow cytometers had only been used to analyze one sample at a time, because putting buffer fluids between samples did not prevent intermixing and because of the above-described problems with using bubbles to separate samples.

For the reasons discussed above, claim 1 is patentable over Parce *et al.*

Hach *et al.* is only cited for disclosing "a pump and a means for periodically injecting a separation gas (air bubbles) in the sample tubing to separate liquids and clean sweep the tubing" as set forth in the March 28, 2001, Office Action at p. 11. (The March 28, 2001, Office Action provides the "reasons of record" referred to in the rejection set forth at paragraph 9 of the September 13, 2001, Office Action). Therefore, Hach *et al.* does not remedy the deficiencies of Parce *et al.* with respect to failing to describe or show claim 1's feature of using a flow cytometer as a detection device and claim 1 is thus patentable over the combination of Hach *et al.* and Parce *et al.*

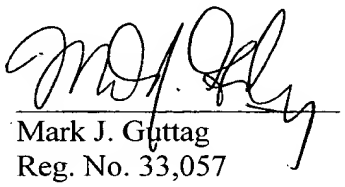
Trinel *et al.* is only cited for disclosing "an automatic flow analysis apparatus wherein samples are separated by intermediate segments of decontamination solution and wherein spacing between the samples and the decontamination solution are effected by segments of an separation inert gas [sic]" as set forth in the March 28, 2001, Office Action at p. 11. (The March 28, 2001, Office Action provides the "reasons of record" referred to in the rejection set forth at paragraph 9 of the September 13, 2001, Office Action). Therefore, Trinel *et al.* does not remedy the deficiencies of Parce *et al.* with respect to failing to describe or show claim 1's feature of using a flow cytometer as a detection device and thus claim 1 is patentable over the combination of Trinel *et al.* and Parce *et al.*

Claims 2-3, 9-12, 15-19, 26-27 and 46-47 depend directly or indirectly from claim 1, and, accordingly, include all of the patentable features of claim 1 as well as other patentable features. Therefore, claims 2-3, 9-12, 15-19, 26-27 and 46-47 are patentable over the combination of Hach *et al.* or Trinel *et al.* with Parce *et al.* for the reasons discussed above with respect to claim 1.

If the Examiner has any questions or concerns regarding the present response, the Examiner is invited to contact Mark J. Guttag at 703-591-2664.

In view of the foregoing, it is respectfully submitted that this application is in condition for allowance, and favorable action is respectfully solicited.

Respectfully submitted,



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November 14, 2002

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	)	
	)	
SKLAR *et al.*	)	**Examiner: Gabel, G.**
	)	
Serial Number: 09/501,643	)	**Art Unit: 1641**
	)	
Filed: February 10, 2000	)	
	)	
For: FLOW CYTOMETRY FOR HIGH THROUGHPUT SCREENING	)	**Docket No.: UNME-0070-1**
	)	

Director of the U.S. Patent and Trademark Office
Washington, D.C. 20231

VERSION WITH MARKINGS TO SHOW CHANGES MADE

Sir:

Below are the amendments in the accompanying Amendment for the above-identified application shown in redlined format:

IN THE CLAIMS

Please amend the claims, without prejudice or disclaimer, as indicated below:

1. (Three Times Amended) A flow cytometry apparatus for the detection of particles from a plurality of samples comprising:

means for moving the plurality of samples comprising particles from a plurality of respective source wells into a fluid flow stream, said means for moving the plurality of samples comprising a pump;

means for introducing a separation gas between each of said plurality of samples in said fluid flow stream; and

a flow cytometer for hydrodynamically focusing said fluid flow stream and selectively analyzing said particles in each of said plurality of samples as said fluid flow stream passes through said flow cytometer.

2. The flow cytometry apparatus of claim 1, wherein said means for moving said plurality of samples further comprises an autosampler.

3. The flow cytometry apparatus of claim 2, wherein said autosampler includes a probe and said flow cytometry apparatus includes a means for exposing a probe tip of said probe to a jet of gas to remove liquid from said probe tip.

4. The flow cytometry apparatus of claim 2, wherein said autosampler includes a probe having a conical tip.

5. The flow cytometry apparatus of claim 2, wherein said autosampler includes a hydrophobic probe.

6. The flow cytometry apparatus of claim 5, wherein said probe comprises a hydrophobic material.

7. The flow cytometry apparatus of claim 5, wherein said probe is coated with a hydrophobic material.

9. (Twice Amended) The flow cytometry apparatus of claim ~~1~~10, wherein a portion of said fluid flow stream passing through said peristaltic pump is contained within~~said tube comprises~~ a high speed multi-sample tube.

10. The flow cytometry apparatus of claim 1, wherein said pump comprises a peristaltic pump.

11. The flow cytometry apparatus of claim 10, further comprising a single length of tubing extending from said autosampler to said flow cytometer.

12. The flow cytometry apparatus of claim 11, wherein said single length of tubing comprises a high speed multi-sample tube.

13. (Three Times Amended) The flow cytometry apparatus of claim 12, wherein said high speed multi-sample tube comprises a poly vinyl chloride tube.

14. (Three Times Amended) The flow cytometry apparatus of claim 12, wherein said high speed multi-sample tube comprises a poly vinyl chloride tube having an inner diameter about 0.02 inches and a wall thickness of about 0.02 inches.

15. The flow cytometry apparatus of claim 1, wherein said separation gas comprises air.

16. The flow cytometry apparatus of claim 1, wherein said plurality of samples are homogenous.

17. The flow cytometry apparatus of claim 1, wherein said plurality of samples are heterogeneous.

18. The flow cytometry apparatus of claim 1, wherein said particles comprise biomaterials.

19. The flow cytometry apparatus of claim 18, wherein said biomaterials are fluorescently tagged.

20. The flow cytometry apparatus of claim 1, further comprising a well plate including said plurality of respective source wells.

21. The flow cytometry apparatus of claim 20, wherein said well plate includes at least 96 source wells.

22. The flow cytometry apparatus of claim 20, wherein said well plate includes at least 384 source wells.

23. The flow cytometry apparatus of claim 20, wherein said well plate includes at least 1536 source wells.

24. The flow cytometry apparatus of claim 20, wherein said well plate includes wells having a conical shape.

25. The flow cytometry apparatus of claim 20, wherein said well plate is mounted in an inverted position.

26. (Amended) The flow cytometry apparatus of claim 1, further comprising a means for injecting a buffer fluid between adjacent samples in said fluid flow stream so that said adjacent samples are separated by two bubbles of separation gas and said buffer fluid located between said two bubbles of separation gas.

27. The flow cytometry apparatus of claim 1, wherein at least one of said plurality of samples includes a drug present therein.

46. (Amended) The flow cytometry apparatus of claim 1, wherein a portion of said fluid flow stream passing through said pump is contained within a tube having an internal diameter of 0.02 inches ~~or less~~.

47. (Amended) The flow cytometry apparatus of claim 10, wherein a portion of said fluid flow stream passing through said peristaltic pump is contained within a tube having an internal diameter of 0.02 inches ~~or less~~.